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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/489,760	01/21/2000	Elsa A. J. M. Goulmy	4285us	6225

7590 01/29/2003

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	24

DATE MAILED: 01/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/489,760	Applicant(s) GOULMY ET AL.	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

-- Th MAILING DATE of this communication app ars on the cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 20-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 20-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/4/02 has been entered.

2. Claims 1-5 and 20-24 are pending and are being acted upon in this Office Action.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-5 and 20-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) a peptide consisting of 9 amino acids constituting a T-cell epitope obtainable from the minor Histocompatibility antigen HA-1, said peptide consisting of the sequence VLXDDLLEA (SEQ ID NO: 1) wherein X represents a histidine or an arginine residue for diagnosing minor Histocompatibility antigen (HA-1) incompatibility between donor and recipient of bone marrow transplant using in vitro CTL assays (See pages 5, 7, 14-17, 25-26 of the specification), generation of VLHDDLLEA or VLRDDLLEA specific CTL *in vitro* for adoptive immunotherapy, **does not** reasonably provide enablement for (1) *any* peptide "**having**" 9 amino acids constituting a T-cell epitope obtainable from the minor Histocompatibility antigen HA-1, said peptide "**having**" the sequence VLXDDLLEA (SEQ ID NO: 1), wherein X represents a histidine or an arginine residue, (2) *any* immunogenic polypeptide "**having**" 9 amino acids obtainable from the minor Histocompatibility antigen HA-1, said immunogenic polypeptide "**having**" the sequence VLXDDLLEA (SEQ ID NO: 1), wherein X represents a histidine or an arginine residue, (3) the immunogenic polypeptide "**having**" 9 amino acids obtainable from the minor Histocompatibility antigen HA-1, said immunogenic polypeptide "**having**" the sequence VLXDDLLEA (SEQ ID NO: 1), wherein X represents a histidine residue, (4) *any* preparation for stimulating the immune response comprising the immunogenic polypeptide "**having**" 9 amino acids obtainable from the minor Histocompatibility antigen HA-1, said immunogenic polypeptide

"**having**" the sequence VLXDDLLEA (SEQ ID NO: 1), wherein X represents a histidine or an arginine residue, (5) any pharmaceutical formulation comprising the immunogenic polypeptide "**having**" 9 amino acids obtainable from the minor Histocompatibility antigen HA-1, said immunogenic polypeptide "**having**" the sequence VLXDDLLEA (SEQ ID NO: 1), wherein X represents a histidine or an arginine residue, (6) the peptide "**having**" 9 amino acids constituting a T-cell epitope obtainable from the minor Histocompatibility antigen HA-1, said peptide "**having**" the sequence VLXDDLLEA (SEQ ID NO: 1), wherein X is a histidine residue, (7) *any* preparation for stimulating the immune response comprising the peptide "**having**" 9 amino acids constituting a T-cell epitope obtainable from the minor Histocompatibility antigen HA-1, said peptide "**having**" the sequence VLXDDLLEA (SEQ ID NO: 1), wherein X represents a histidine or an arginine residue, (8) the preparation for stimulating the immune response comprising the immunogenic polypeptide "**having**" 9 amino acids obtainable from the minor Histocompatibility antigen HA-1, said immunogenic polypeptide "**having**" the sequence VLXDDLLEA (SEQ ID NO: 1), wherein X is a histidine, (9) *any* pharmaceutical formulation comprising the peptide "**having**" 9 amino acids constituting a T-cell epitope obtainable from the minor Histocompatibility antigen HA-1, said peptide "**having**" the sequence VLXDDLLEA (SEQ ID NO: 1), wherein X represents a histidine or an arginine residue, and (10) The pharmaceutical formulation comprising the immunogenic polypeptide "**having**" 9 amino acids obtainable from the minor Histocompatibility antigen HA-1, said immunogenic polypeptide "**having**" the sequence VLXDDLLEA (SEQ ID NO: 1), wherein X is a histidine residue for preventing graft versus host disease or to treat any HA-1 related autoimmune disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only two peptides of minor Histocompatibility antigen HA-1. The peptides are VLHDDLLEA (SEQ ID NO: 2) and VLRDDLLEA (SEQ ID NO: 5) wherein the peptides having a structure of nine amino acids in length for diagnosing incompatible minor Histocompatibility antigen HA-1 associated with bone marrow transplant and generating HA-1 specific CTLs ex-vivo.

The specification does not teach how to make any peptide or any immunogenic polypeptide "having" 9 amino acids constituting a T-cell epitope from minor Histocompatibility antigen HA-1, much less how to use any peptide and immunogenic polypeptide because the term "having" is open-ended. It expands the peptide and the immunogenic polypeptide to include additional amino acid residues at either or both ends of said peptide or immunogenic polypeptide. There is insufficient guidance as to the undisclosed amino acids to be added, and whether the resulting peptide or immunogenic polypeptide after addition would retain both structure and function as SEQ ID NO: 1 wherein X represents a histidine or an arginine residue. Given the indefinite of undisclosed amino acid to be added, there are insufficient in vivo working examples demonstrating that any undisclosed peptide and immunogenic polypeptide are effective for a pharmaceutical formulation for induction of tolerance or vaccines in HA-1 related autoimmune diseases.

Stryer *et al* teach a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed relevant pages).

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Colman *et al* (of record) teach that even a single amino acid difference in an antigen can abolish the antibody-antigen interaction entirely (page 33, in particular).

Tisch *et al* teach peptide/antigen-specific immunotherapy is not feasible in prevention of spontaneous autoimmune disease such as Rheumatoid arthritis (RA), in which the target autoantigen(s) is not known and a number of autoantigens appear to be involved in the disease process (See page 437, column 2, first full paragraph, in particular).

Anderton *et al* teach that peptide-based immunotherapy for autoimmunity is unpredictable, for instance, systemic application of peptides PLP (139-151) or MOG (35-55)

resulted in EAE. However, the same peptides given intraperitoneally after disease resolution resulted in anaphylaxis and death (page 373, first column, first full paragraph, in particular).

Peakman *et al* teach antigen-specific immunotherapy for human autoimmune disease is currently limited by several constraints. First, it requires the accurate definition of critical disease-related epitopes and their T-cell contact residues. Second, it requires experimental evidence of efficacy in antagonizing appropriate T cells (See page 363, column 2, second full paragraph, in particular), the timing of the therapy (See page 364, column 1, in particular), safety, especially the potential for precipitating, exacerbating or inducing de novo autoimmune disease (See page 364, column 1, in particular).

Given the indefinite number of peptide and immunogenic polypeptide for induction of tolerance or vaccines in HA-1 related undisclosed autoimmune diseases and since the therapeutic indices of autoimmune diseases can be species- and model-dependent, a pharmaceutical formulation in the absence of in vivo data are unpredictable for the following reasons: (1) the peptide or polypeptide may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the peptide or polypeptide; (2) the peptide or polypeptide may not reach the target area because, i.e. the peptide or polypeptide may not be able to cross the mucosa or the peptide or polypeptide may be adsorbed by fluids, cells and tissues where the peptide or polypeptide has no effect; and (3) other functional properties, known or unknown, may make the peptide or polypeptide unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 12/4/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) claims 1 and 2 have been amended to recite a peptide or an immunogenic polypeptide, respectively, having 9 amino acids...having the sequence

VLXDDLLEA (SEQ ID NO: 1). Since the specification is enabled for the peptide and immunogenic polypeptide having 9 amino acids of SEQ ID NO: 1, the claims should be considered enabled. (2) The amendment to claims 1 and 2 should obviate the non-enablement for any Vaccine or any "pharmaceutical formulation" against Graft versus host disease or treating any HA-1 related autoimmune disease.

However, the term "having" in amended claims 1 and 2 is open-ended. It expands the peptide and the immunogenic polypeptide to include additional amino acid residues at either or both ends of said peptide or immunogenic polypeptide. There is insufficient guidance as to the undisclosed amino acids to be added, and whether the resulting peptide or immunogenic polypeptide after addition would retain both structure and function as SEQ ID NO: 1 wherein X represents a histidine or an arginine residue. Given the indefinite of undisclosed amino acid to be added, there are insufficient in vivo working examples demonstrating that any undisclosed peptide and immunogenic polypeptide are effective for a pharmaceutical formulation for induction of tolerance or vaccines in HA-1 related autoimmune diseases.

Further, claims 5, 23 and 24 still recite a "pharmaceutical formulation". The said "pharmaceutical formulation" comprises *any* peptide or any polypeptide "having" an indefinite number of undisclosed amino acids at either or both ends of SEQ ID NO: 1 for induction of tolerance or vaccines in HA-1 related autoimmune diseases. Given the indefinite number of peptide and immunogenic polypeptide for induction of tolerance or vaccines in HA-1 related undisclosed autoimmune diseases and since the therapeutic indices of autoimmune diseases can be species- and model-dependent, a pharmaceutical formulation in the absence of in vivo data are unpredictable for the following reasons: (1) the peptide or polypeptide may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the peptide or polypeptide; (2) the peptide or polypeptide may not reach the target area because, i.e. the peptide or polypeptide may not be able to cross the mucosa or the peptide or polypeptide may be adsorbed by fluids, cells and tissues where the peptide or polypeptide has no effect; and (3) other functional properties, known or unknown, may make the peptide or polypeptide unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

5. Claims 1-5 and 20-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification discloses only two peptides of minor Histocompatibility antigen HA-1. The peptides are VLHDDLLEA (SEQ ID NO: 2) and VLRDDLLEA (SEQ ID NO: 5) wherein the peptides having a structure of nine amino acids in length for diagnosing incompatible minor Histocompatibility antigen HA-1 associated with bone marrow transplant and generating HA-1 specific CTLs ex-vivo.

The specification does not reasonably provide a **written description** of (1) *any* peptide or (2) *any* immunogenic polypeptide "**having**" 9 amino acids constituting a T-cell epitope obtainable from the minor Histocompatibility antigen HA-1, said peptide "**having**" the sequence VLXDDLLEA (SEQ ID NO: 1), wherein X represents a histidine or an arginine residue for preventing graft versus host disease or to treat any HA-1 related autoimmune disease because the term "having" is open-ended. It expands the peptide or immunogenic polypeptide to include additional amino acid residues at either or both ends of said peptide of immunogenic polypeptide.

With the exception of the specific peptide or immunogenic polypeptide consisting of SEQ ID NO: 1, there is insufficient written description about the structure associated with function of (1) *any* peptide or (2) *any* immunogenic polypeptide "**having**" 9 amino acids constituting a T-cell epitope obtainable from the minor Histocompatibility antigen HA-1, said peptide "**having**" the sequence VLXDDLLEA (SEQ ID NO: 1), wherein X represents a histidine or an arginine residue, much less for preventing graft versus host disease or to treat any HA-1 related autoimmune disease.

Given the lack of a written description of *any* additional representative species of peptide or immunogenic polypeptide, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 12/4/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) claims 1 and 2 have been amended to recite a peptide or an immunogenic polypeptide, respectively, having 9 amino acids...having the sequence VLXDDLLEA (SEQ ID NO: 1). Since the specification is enabled for the peptide and immunogenic polypeptide having 9 amino acids of SEQ ID NO: 1, the claims should be considered enabled. (2) The amendment to claims 1 and 2 should obviate the non-enablement for any Vaccine or any "pharmaceutical formulation" against Graft versus host disease or treating any HA-1 related autoimmune disease.

However, the term "having" in amended claims 1 and 2 is open-ended. It expands the peptide and the immunogenic polypeptide to include additional amino acid residues at either or both ends of said peptide or immunogenic polypeptide. There is insufficient written description about the structure of any peptide or polypeptide having additional undisclosed amino acids in addition to the amino acids already in SEQ ID NO: 1, much less having the same function, in turn, for a pharmaceutical formulation for induction of tolerance or vaccines in HA-1 related autoimmune diseases.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

7. Claims 1-2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "having" in claims 1-2 is indefinite and ambiguous. The Office interprets "having" as "comprising", which is open-ended. If the claimed peptide is intended to be open-ended, it is suggested that Applicant amends the claims to recite a peptide "comprising". If the claimed peptide is intended to be close, it is suggested that the Applicant amends the claims to recite a peptide "consisting of".

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

10. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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January 27, 2003

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